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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Applicant's copy

Office Action Summary

Application No.	Applicant(s)
09/393,803	Liu et al
Examiner	**Group Art Unit**
Jon Shuman	1636

☒ Responsive to communication(s) filed on *Preamendment B of September 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-44* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☒ Claim(s) *23* is/are allowed.

☒ Claim(s) *1-22 and 24-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

This action is responsive to the preamendments of 10 September 1999.

Claims 1-44 are pending.

Applicant is strongly encouraged to submit, with the response to this office action, a clean copy of the claims. The line numbering of the paper used appears within the claims, leading to confusion. Please submit a clean copy of the claims wherein the line numbers do not insert into the claims.

Applicant is further advised of a problem with the Brief Description of the Drawings, at page 8. There are two legends for figure 15, but only one figure on one sheet. Clarification and correction is required.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The relationship of the instant application to the 08/207,526 application claimed under 35 U.S.C. 120 on the oath, is not stated in the continuing data at page one of the specification. It is suggested that the continuing data be amended to include this information.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is indefinite in that it reads as if only one polynucleotide construct was being claimed. However, it is unclear whether the constructions set forth as a) through n) are designating different vector constructions, or are enumerating pieces of a singular construction. Thus, the scope of the invention applicant intends to claim cannot be properly ascertained. Appropriate correction is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 12, 13, 14, 15, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Almond et al (WO93/11250, published 10 June 1993) or Almond et al, (GB 2 262 099A, May 12, 1991) in view of (Ulmer et al, Science Vol. 259, pages 1745-49, March 1993) and Woo et al (U.S. Patent 5,674,703, December 2, 1993).

Applicants claim a polynucleotide which is "non-replicating", and induces the co-expression of at least two gene products, wherein the construct has a first eukaryotic promoter operatively linked to a first cistron, and a second cistron operatively controlled by the first promoter or by its own promoter, and optionally, a third cistron downstream of the second cistron, operatively controlled by either the first promoter, the second promoter, or a third promoter, further containing transcriptional terminators when a promoter precedes a following cistron. The first cistron may encode an immunogenic epitope of a pathogen, which may be viral in origin, particularly from HIV. The second citron may encode any HIV gene product, particularly REV. The third cistron may encode a cytokine, or any T-cell costimulatory product, particularly a B7 protein. These embodiments may be encoded in any particular order or permutation. When the second and/or third cistron does not include a transcriptional promoter, an internal ribosome entry site (henceforth IRES) or ribosome landing pad is inserted between the two elements. The IRES may be from the encephalomyocarditis virus (EMCV), swine vesicular virus, or poliovirus. In a particular embodiment, the REV gene may be spliced. Applicants claim the constructions wherein an HIV-1 epitope is encoded with a cytokine and a T-cell co-stimulatory molecule. In one embodiment, the co-stimulatory molecule is B7. Further, a method of using the composition is claimed, wherein it is introduced into the tissue of a vertebrate.

Almond et al (both) disclose a polynucleotide construction (page 4, top) which induces the expression of at least two gene products. The construction has at least a first eukaryotic promoter followed by a first cistron and a second cistron under the control of the first promoter,

wherein an IRES is inserted between the two constructions. The first cistron encodes an immunogenic epitope of a pathogen and is viral in origin. The second gene expresses an epitope that is "foreign" to the product encoded by the first cistron. The sequences are noted to be encoded in either order (page 4, lines 11-16). The IRES or ribosome landing pad sequences of EMCV and poliovirus are disclosed (page 5, lines 15-23). The use of the construction as a vaccine is also disclosed (page 6, lines 17-20), and the desirability of expressing in such a construction a polypeptide that may induce either a T or a B cell response, or both is disclosed (page 6, lines 20-25). The possibility of raising a neutralizing antibody to a pathogen is a further embodiment of the disclosure (p6, lines 23-30). Antigens of the HIV virus, either HIV-1 or HIV-2 are disclosed as potential products for expression by the construction (page 6, lines 27-35). Additionally, the co-expression of proteases and growth factors is also disclosed (page 7, lines 1-10), as it is well known to one of skill in the art that growth factors and co-receptors or co-stimulatory molecules play an important role in the immune response to foreign antigens. Almond et al does not teach that the construction is non-replicating or that the construction may contain three separate promoters.

Ulmer et al teach that polynucleotides can be introduced into cells essentially as "naked" or nonreplicating DNA, wherein the encoded proteins are expressed and act as an immunogen. Ulmer discloses the drawbacks of using replicating vectors to produce proteins as antigens in cells (page 1746, column 1) as well as the problems attendant to the injection of peptides into the cytosol (page 1746, column 1). "Hence, immunization with nonreplicating plasmid DNA

encoding viral proteins may be advantageous because no infectious agent is involved, no assembly of virus particles is required, and determinant selection is permitted" (page 1746, column 1). Additionally, a method of introducing the construction for vaccination is disclosed.

Woo et al teach a polynucleotide construction (page 4, top) which induces the expression of at least two gene products. The construction has at least a first eukaryotic promoter followed by a first cistron and at least a second cistron under the control of at least a second eukaryotic promoter, wherein the polynucleotide construction encodes at least a third cistron preceded by at least a third eukaryotic promoter (see claim 1). The promoters may each be the same or different, in any particular order (column 9, last paragraph). The desirability of coordinate expression is further disclosed at column 10, wherein an internal ribosome binding site of the EMCV or polio virus is disclosed, as is the utility of a polycistronic mRNA. The property of having a transcriptional terminator between transcription units is inherent to the constructions. Each cistron encodes a polypeptide, one of which encodes an immunogenic epitope of a pathogen. Additionally, one of the citrons encodes a gene product that is therapeutic, eg. a growth factor or chemokine or interleukin. Woo does not teach that the polynucleotide construction is "non-replicating".

It would have been obvious to one of ordinary skill in the art, seeking to develop a safe, reliable method of producing immunity against a polypeptide, to combine the teachings of Almond et al with regard to the use of IRES sequences for the coordinate expression of two gene products on a bi-cistronic mRNA, with the teachings of Ulmer et al with regards to the desirability of using

nonreplicating DNA as an immunogen. One would have been motivated to do this for the known and expected properties of nonreplicating DNA immunogens, expression of immunogenic epitopes in the absence of replication or perpetuation of the DNA inoculum, thereby providing both a specific and a safe immunogen. The problems of immune neutralization of viral vectors commonly encountered upon re-administration or "boosting" are well known to one of ordinary skill in the art of gene therapy, as acknowledged by applicants in the instant specification, due to continuous expression of foreign (viral) epitopes, against which a strong immune response is mounted. In addition, the potential hazards that are inherent in the use of replicating viral constructions, due to their ability to integrate and/or recombine with the host chromosome, are known in art and acknowledged in the instant specification. The nonreplicating DNA approach and methods of administering, is noted for avoiding each of these drawbacks to conventional viral vector approaches. Other limitations such as expressing cytokines and co-stimulatory proteins are well known in the art and are thus obvious variables when optimizing immune stimulation. The order of sequences encoded within the vector has been addressed, and it is further deemed obvious that if two sequences function in a bicistronic message, that three sequences would function similarly. Given the teachings of the prior art and the knowledge of one of ordinary skill in the art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Thus, the invention as a whole was *prima facie* obvious at the time the invention was made.

It would have been obvious to one of ordinary skill in the art, seeking to develop a safe, reliable method of producing immunity against a polypeptide, to combine the teachings of Woo et al with regard to the use of multiple eukaryotic promoters for the coordinate expression of at least two gene products, with the teachings of Ulmer et al with regards to the desirability of using nonreplicating DNA as an immunogen. One would have been motivated to do this for the known and expected properties of nonreplicating immunogens, expression of immunogenic epitopes in the absence of replication or perpetuation of the DNA inoculum, thereby providing both a specific and a safe immunogen. The problems of immune neutralization of viral vectors commonly encountered upon re-administration or "boosting" are well known to one of ordinary skill in the art of gene therapy, as acknowledged by applicants in the instant specification, due to continuous expression of foreign (viral) epitopes, against which a strong immune response is mounted. In addition, the potential hazards that are inherent in the use of replicating viral constructions, due to their ability to integrate and/or recombine with the host chromosome, are known in art and acknowledged in the instant specification. The nonreplicating DNA approach is noted for avoiding each of these drawbacks to conventional viral vector approaches. Other limitations such as expressing ligands for T cell co-stimulatory proteins, cytokines or growth factors are deemed inherent to immune stimulation and are obvious variables to test, and well known in the art. The strategy of such an approach for providing immunity against viral antigens is well known in the art and described above. Given the teachings of the prior art and the knowledge of one of ordinary skill in the art, it must be considered that the ordinary skilled artisan would have had a reasonable

expectation of success in practicing the claimed invention. Thus, the invention as a whole was *prima facie* obvious at the time the invention was made.

5. Claims 6-11, 16-22, 35, 39-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Almond et al (WO93/11250, published 10 June 1993) or Almond et al, (GB 2 262 099A, May 12, 1991) in view of Ulmer et al (Science Vol. 259, pages 1745-49, March 1993) and Woo et al (U.S. Patent 5,674,703, December 2, 1993) as applied to claims 1-5, 12-15 and 25, and further in view of Schwartz et al (Schwartz et al, Virology, Vol. 183, pages 677-686, 1991) or Smarda et al (Gene Vol. 137, pages 145-149, 1993).

Applicants invention was described above. In addition, applicants claim the invention wherein REV protein is utilized to provide for efficient expression of genes encoded on a polycistronic messenger RNA. As above, applicants claim the construction wherein a T-cell costimulatory protein is expressed and/or a cytokine. Applicants further claim constructions wherein the REV product is spliced. Applicants claim a method for co-expression in vivo of at least two gene products using the constructions. Further, applicants claim the construction wherein the HIV-1 epitope is spliced, and contains an RRE, followed by an IRES and REV where REV is also spliced. Applicants further claim appending a heterologous leader sequence appended to the HIV-1 epitope either with or without the REV binding element, RRE. Applicants also claim individual expression constructs, each mixed together, and then list each open reading frame of HIV-1.

The teachings of Almond et al, Ulmer et al., and Woo et al were described above, and do not teach the use of the REV gene product for efficient expression of genes encoded on a polycistronic mRNA.

Schwartz et al teach that HIV-1 mRNAs are subject to positive or negative regulation by the REV protein (page 677, column 2). Schwartz teaches that "REV binds to an RNA site within the env region, named the REV-responsive element (RRE). This element was also named CAR. REV promotes the transport and efficient translation of partially spliced HIV mRNAs containing the RRE. In contrast, REV down regulates the levels of all multiply spliced mRNA species missing RRE." (Page 677, column 2). Schwartz also teaches the genomic organization of HIV-1 virus (figure 1, page 679). The processing of the envelope glycoprotein, and the splicing of the REV protein are well known to those of skill in the art, as acknowledged in the instant specification.

It would have been obvious to one of ordinary skill in the art, seeking to efficiently translate proteins encoded on a polycistronic mRNA, to combine the teachings of Almond et al with regard to the use of IRES sequences for the coordinate expression of two gene products on a bi-cistronic mRNA, with the teachings of Ulmer et al with regards to the desirability of using nonreplicating DNA as an immunogen and the teachings of Schwartz et al with regards to the function of REV as a protein that promotes the export and efficient translation of partially spliced HIV mRNAs containing the RRE . One would have been motivated to do this for the known and expected properties of the REV protein with respect to mRNAs containing its binding site, the

REV response element or RRE, efficient export of unspliced mRNA from the nucleus, coupled with efficient translation of the mRNA. This strategy is one known to those skilled in the art as the one utilized by the HIV-1 virus as a mechanism to provide for efficient expression of the viral proteins. Other limitations such as expressing ligands for T cell co-stimulatory proteins, cytokines or growth factors are well known in the art and are thus obvious variants to optimize for immune stimulation.

It would have been obvious to splice the REV gene transcript, because the REV gene transcript is spliced by the HIV genome itself. It is well known to those of skill in the art that splicing may result in more efficient gene expression in eukaryotic cells. Thus, one would be motivated to test both spliced and un-spliced REV expression in order to optimize for optimal REV expression, and the resulting efficient expression of the co-expressed products.

It would have been obvious to provide both the immature and mature forms of the envelope glycoprotein by splicing, because the envelope glycoprotein is proteolytically processed by the HIV-1 virus, such that both the 160 and 120 KDa forms are known. Thus, it is obvious to test one known product for another, in order to optimize for the most immunogenic form of the protein.

It would have been obvious to append an heterologous leader peptide sequence to the envelope glycoprotein, because the goal is to over-produce the protein for efficient immune presentation. It is well known in the art that well expressed leader peptide sequences can lead to more efficient over-production of a protein. One would have been motivated to do this because

more efficient expression generally leads to better immune presentation, and hence better immunogenicity. Thus, one is optimizing known parameters that lead to efficient protein expression, and thus optimizing within a range.

It would have been obvious to separate the constructions onto individual polynucleotides, because individual constructions are functional equivalents of the polycistronic polynucleotide constructions, and it is obvious to substitute one functional equivalent for another.

It would have been obvious to test one or two or three of the known HIV-1 gene products together in the construction, because one does not know a priori which construction will work. In order to find the proper combination, one would vary all the known gene products, as an obvious optimization strategy. Given the teachings of the prior art and the knowledge of one of ordinary skill in the art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Thus, the invention as a whole was *prima facie* obvious at the time the invention was made.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 26-34, 36-38 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (Haynes, Science Vol. 260, pages 1279-1286, 1993)

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with the information known in the art without undue experimentation (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. In *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the Court described the standard of undue experimentation as a standard of reasonableness and set forth the various factors to be considered in the determination of enablement for a claimed invention. These factors include the following:

Applicants claim methods of inducing immune responses in vertebrates against HIV epitopes by introducing the polynucleotides compositions described above.

1) Unpredictability of the art. The art of vaccinating a vertebrate host organism against HIV viral infection or viral epitopes is unpredictable. First, at the time of applicant's invention, there was no model organism that exhibited an immune response to HIV that was correlative with that of humans. It is known in the art that the surface antigens of the virus mutate rapidly, thus evading immune responses and that no protective immunity has been raised, even to date. Thus, the art of vaccinating a vertebrate against HIV infection is unpredictable.

2) State of the art. The art of vaccinating vertebrate organisms against viral infections, at the time of applicant's invention, was well developed. However, the unique challenges presented by the HIV virus through attacking the helper T cell subset present heretofore insurmountable challenges. "The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use" (Haynes, page 1279, column 1). "Although more is known about HIV than almost any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventative vaccine" (Haynes, page 1279, column 3). Further, there are no animal models for human infection. "Because of a lack of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known" (page 1280, column 1). Thus, the state of the art, although high, remains underdeveloped, and extensive experimentation of a discovery nature is ongoing.

3) Number of working examples. Although Applicants test various polynucleotide constructions in mice and primates, these systems are not acknowledged models that would reflect the human condition, as noted by Haynes, which is presented to show what one skilled in the art would have expected at the time the invention was made. Additionally, the primate system tested by applicants did not demonstrate protective immunity. One can only conclude that trial and error experimentation must be undertaken in order to develop HIV vaccines, and that such experimentation is not considered routine.

4) Amount of guidance presented by applicants. Applicants present many permutations on a given theme that can be tried, in an effort to develop a safe and effective HIV vaccine. However, given the unique course of HIV infection and its subsequent attack of the host immune system, highly detailed guidance would be necessary to enable one of ordinary skill in the art to practice the claimed invention in the vaccination of humans against HIV. Applicants must provide sufficient guidance to teach one of skill in the art to make and use the invention, inclusive of the full scope of the claims.

5) Scope of the claims. Claims 26-34, 36-38 and 43, given the broadest reasonable interpretation, encompass the vaccination of any vertebrate against HIV. Absent evidence to the contrary, applicants own data show that vaccination of primates using the instant strategy failed. Further, no vaccine against HIV has been developed, to date. Thus, the scope of the claim is very broad.

6) Nature of the invention. The invention involves the complex interaction of the host immune system with polynucleotide composition used in a method of vaccinating against HIV. Absent evidence that the immune systems of all host organisms respond to the above described polynucleotide compositions with identical immune responses which results in protective immunity, it must be considered that the invention encompasses protective immunity in many different host organisms resulting from complex interactions between host immune cells and HIV epitopes. Thus, the invention is directed towards raising protective immunity in any vertebrate against HIV/AIDS, and is thus very highly complex.

7) Level of skill in the art. The level of skill in the art of vaccination is high; however, the challenges that remain before successful human vaccination against HIV are well documented (Haynes). The failure to develop a model organism for human HIV is just one obstacle among many others, that has impeded progress in these diligent efforts. Thus, the level of skill in the art of HIV vaccination, though high, is still underdeveloped.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a given invention is enabled, it must be considered that the skilled artisan would have to have practiced undue and excessive experimentation in order to practice the claimed invention.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Shuman whose telephone number is (703) 306-5819. The examiner can normally be reached on Monday to Friday from 8:00 AM to 4:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon Shuman

April 19, 2000

DAVID GUZO
PRIMARY EXAMINER